Pulmonary Hypertension

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Chief among the features that characterize the circulation in normal man is the low hydrostatic pressure within the pulmonary vascular bed. In a variety of disorders of the heart and lungs, however, an elevation in this pressure occurs. To define the mechanism of its occurrence in a few instances and to relate this finding to the other features of the disease entity concerned is the purpose of these remarks.

1. *The development of pulmonary hypertension.* (a) *As a result of left ventricular failure.* Since there is a certain degree of automaticity of response of each cardiac ventricle to an imposed work load, there may exist some degree of independent activity of each. For example, if, because of disease of the heart muscle, the left ventricle suddenly fails to empty itself to a normal extent with systole and a similar change does not immediately occur on the right, right ventricular output temporarily will exceed that of the left and pulmonary congestion will result. The eventual level to which pulmonary pressures rise because of this shift of blood from the systemic to the pulmonary vascular bed is determined both by the reduction in venous return to the right heart and by the level of end-diastolic pressure on the left which effects an output of this chamber equal to that of the right.

b. *As a result of mitral stenosis.* Changes similar to those described above, but obviously neither so acute nor the same in origin, may occur in the presence of mitral stenosis. Here again it must be emphasized that left atrial, and consequent pulmonary arterial, hypertension when present is not a *compensatory* response of the circulation which serves to maintain an adequate cardiac output in the face of valvular obstruction. It is simply a reflection of the state of equilibrium between the various factors that regulate cardiac output in man and the valvular deformity that impedes blood flow.

c. *As a result of changes in the pulmonary vascular bed.* Direct obstruction of the smaller pulmonary vessels occurring as a result of metastatic carcinoma, multiple pulmonary emboli, and sclerotic changes as commonly seen in severe mitral stenosis may lead to profound pulmonary hypertension. An overall reduction in the number of the smaller vessels as may occur in certain forms of chronic pulmonary disease may have a similar result. Physiologic changes in the vascular bed may occur under certain conditions also. The inhalation of very low oxygen mixtures, for example, will result in pulmonary hypertension in normal man which seems to be out of proportion to the associated increased blood flow and is therefore presumed to be due to vasoconstriction. Finally, anything that tends to increase pulmonary blood flow when any of these obstructive lesions are present will promote further elevation in pulmonary vascular pressures.

2. *The importance of pulmonary hypertension in chronic pulmonary disease.* Pulmonary hypertension as seen in cases of chronic pulmonary disease generally has no single cause. In emphysema, for instance, pulmonary hypertension seems to stem from several interrelated elements. Arterial anoxia and the hypervolemia secondary thereto both tend to increase the cardiac output, and an increased cardiac output in the presence of a vascular bed reduced in size by the disease process (and perhaps affected directly by the anoxia) may lead to hypertension. The nature of the pulmonary disease will determine which of the multiple factors will dominate the picture,

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and the duration and severity of the changes will, of course, determine whether clinical cor pulmonale will result. It is important to remember about this type of pulmonary hypertension, however, that it is only one manifestation of a larger disorder, pulmonary insufficiency, and, often being due more to disordered pulmonary function than to anatomic change, is frequently reversible. Thus, reduction in blood volume and relief of arterial anoxia by improvement of pulmonary performance will often result in a striking decrease in pulmonary arterial pressure and an improvement of cardiac function in cases of pulmonary emphysema with cor pulmonale.

3. *The importance of pulmonary hypertension in mitral stenosis.* One may say that rheumatic heart disease with mitral stenosis has three components: the valvular deformity, alterations in the pulmonary vascular bed and disease of the myocardium, individual patients exhibiting varying degrees of involvement in each category. These three elements are obviously the causes of the two major physiologic defects that characterize the disorder, viz., reduction in cardiac output and elevation in pulmonary pressures and are also, of course, the cause of cardiac failure and cardiac arrhythmias as well. Not so apparent, however, is the relationship between pulmonary hypertension and the other features of the syndrome. For example, although one might expect pressures within the right heart to exert a strong influence in the matter of heart size and cardiac failure, such is not always the case. As was pointed out recently before the New York Heart Association by Drs. M. I. Ferrer and R. M. Harvey, cardiac enlargement as determined by Roentgen-ray may be more or less independent of right heart pressure, large sac-like hearts often being seen in the presence of rather low pressures while x-ray silhouettes smaller or equal in size are often associated with high pressures. Similarly, there exists no predictable relationship between the level of pulmonary and intracardiac pressures and the presence or absence of cardiac failure. The myocardial element of the disease would seem to be the chief determinant in these matters.

Finally, attention must be paid to the role of pulmonary hypertension in the symptom complex of the patient with mitral stenosis who is ambulatory and not in failure, the patient whose heart disease, despite often profound circulatory abnormalities, is manifest chiefly in exertional dyspnea and lack of stamina.

Early fatigue of skeletal muscles during work might be expected if there is serious impairment of the oxygen supply to these muscles or of the removal of products of metabolism. Hence it is not improbable that the diminished endurance of these patients is related to inadequacy of cardiac output.

Dyspnea, however, is not so readily accounted for. It has been thought to be due, in cases such as these, to interference in pulmonary function secondary to pulmonary congestion, yet recent studies in a representative group of ambulatory rheumatic subjects with varying degrees of pulmonary hypertension and reduction in cardiac output have afforded no support for this view. Measuring the lung volumes, pulmonary ventilation at rest and exercise, maximum breathing capacity, and arterial blood gases at rest and after exercise, we were unable to detect evidence of sufficient impairment of ventilatory function in these cases to warrant the assumption that dyspnea is due to ventilatory insufficiency as defined in terms of minute volumes of breathing reserve. Although some hyperventilation was noted at all phases of activity it was of a very mild degree and maximum breathing capacity was essentially unimpaired.

Concluding from these data that dyspnea in these patients is not due to manifest ventilatory insufficiency we must consider other possibilities if we are to relate inadequate cardiac output and pulmonary hypertension to this symptom. Dyspnea on exertion might be a manifestation of excessive fatigue of respiratory muscles during the increased ventilation of exercise, exhaustion occurring at respiratory minute volumes not ordinarily associated with dyspnea, a result of poor blood supply to these muscles. Or it might be related to the effort in breathing experienced by this group of patients, the effort being far out of proportion to the actual minute volume as a result of a decrease in compliance of the lung secondary to increased vascular pressure. Finally, dyspnea in these patients may not be related to air movement at all, but may be simply a type of discomfort resulting from engorgement of blood vessels in the lesser circulation.

It is our belief that an answer to these latter questions cannot be given at this time but must await further study, using newer methods of measuring the various physical aspects of breathing.

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DISCUSSION

ANDRE COURNAND: It is a pleasure to discuss the paper of Dr. Liebow, since his interests are not limited to problems of pathologic morphology, but rather extend to the physio-pathology of the pulmonary circulation. Such a dual interest is of particular value for the understanding of the problems related to the collateral circulation in the lungs.

A first question arises concerning the method used in order to demonstrate anastomoses between bronchial and pulmonary vessels. To the non-initiated it would seem that only anastomoses of relatively large size can be visualized by this injection technique. Does the contrast material outline the *bronchiolar* veins of very small size which drain into the pulmonary veins?

A second question is whether the mechanism whereby bronchial collateral circulation develops in bronchiectasis applies to other pathologic conditions, such as pulmonary fibrosis or emphysema, since in these disease entities granulation tissues and inflammatory reactions in the bronchial tree are not a dominant feature. Incidentally, it might be interesting to speculate how significant an oxygen supply is provided by the large bronchial collateral circulation observed in bronchiectasis. A simple calculation indicates that blood recirculating in the lung cannot, via the bronchial circulation, take up more than 20 cc. per liter, for each of 10 per cent of oxygen unsaturation.

A third question is raised in my mind as to the validity of the technique of angiocardiography to support the argument that in some instances the circulation in one lung may be much greater than in the other. Does a single film exposure necessarily give adequate information concerning the relative circulation in both lungs? The method of selective angiography developed recently in Germany, by Bolt,[1] which permits the visualization of all segmental branches of the pulmonary artery after their selective catheterization gives much more information on this point.

Regarding the state of the left ventricle in cor pulmonale, I doubt very much the statement that it is commonly found to be hypertrophied or dilated; all physiologic evidences gathered in my laboratory and in others, in the course of studies of patients with cor pulmonale, indicate that the end-diastolic pressure in the left ventricle is presumably normal, and that pulmonary venous congestion does not play any part in the development of pulmonary arterial hypertension.

As a last question, I should like to have Dr. Liebow express an opinion concerning the studies of Von Hayek[2] on the control of the circulation between the small pulmonary vessels and the bronchial arteries by special vessels with marked circular muscular development in their wall, permitting their closure or opening, the so-called "sperr-arterien."

My discussion of Dr. West's paper will be confined to the effect of anoxia upon the pulmonary arterial pressure, about which he purposely was brief.

Von Euler and Liljestrand[3] demonstrated the hypertensive effect of anoxia upon the pulmonary circulation; this was confirmed in man the same year in my laboratory. In the cat the pulmonary arterial hypertension due to anoxia persists after elimination of all autonomous supply to the pulmonary vessels. What the exact mechanism of this effect is has not yet been clearly demonstrated. Apparently the increase in cardiac output following anoxia is not significant enough to cause pulmonary hypertension, and the pressure on the pulmonary venous side remains unaltered. In a series of papers recently published, Nisell[4] has analyzed the action of oxygen and carbon dioxide upon the bronchioles and small vessels of the lungs. From these studies he concluded: 1) That respiratory gases brought into contact with the pulmonary vascular bed by way of the bronchial tree affected pulmonary vascular resistance differently than if the same gases reached the lungs through the blood stream; 2) that both gases may have opposite effects upon the small vessels; and 3) that by their action upon pulmonary elastance they may affect pulmonary vascular resistance. Apparently local effects of respiratory gases upon the small vessels, rather than ganglionic reflexes, are involved in these complex actions.

Further studies are in order to elucidate these mechanisms and to solve in general the important question as to the role played by vasomotricity in the control of the pulmonary vascular pressures. Personally I have held to the concept that hemodynamic changes in the pulmonary vascular bed could be explained under usual physiologic circumstances on a mechanical basis, without resorting to vasomotor regulation. But concepts, after all, can be revised in the light of new experiments. Although it would appear that occasionally vasomotor action upon the pulmonary arteries may persist beyond early infancy and eventually play a role in certain congenital anomalies, pulmonary hypertension, on that basis, seems the exception rather than the rule.

AVERILL A. LIEBOW: For many years Dr. Cournand has illuminated with his brilliance various dark corners of cardiopulmonary physiology, and all of us here who have been interested in this subject have been his students. He has again asked many penetrating questions, some dealing with anatomic and others with functional matters.

The first concerned the so-called normal communications. There have been differences of opinion on this subject. The methods employed in the present study are capable of injecting vessels no smaller than 50 mμ. We have not seen any evidence that anastomoses larger than this exist under normal circumstances.

Dr. Cournand asked about the mechanisms of development and "usefulness" of these bronchial vessels. Although nature usually seems to do the best she can at any particular time, her efforts sometimes do not turn out too well. Actually the bronchial arterial collateral, except possibly as it is a mechanism for shunting blood away from diseased tissue, seems useless or even definitely harmful. There are certain factors that tend to stimulate collateral circulation. For example, there develops in fibrosing pneumonitis a great deal of granulation tissue supplied both from the bronchial and pulmonary vessels. This is one source of capillary supply distal to the arteries. Then there are also considerable degrees of proliferation, both in muscle and lymphoid tissue, that could not exist were there not a supply of oxygenated blood from the bronchial arteries. How this "need" stimulates the growth of the vessels is still unknown. Interestingly enough, as time goes on, this apparently useless collateral in some cases, but not in all, is diminished—and by an interesting mechanism, not merely through thrombosis or endothelial proliferation, but by a tremendous muscular hypertrophy and hyperplasia. I fear that what many have called "sclerotic" pulmonary vessels are in reality such bronchial vessels, characterized by the presence of a very thick longitudinal muscular coat that has encroached upon or even obliterated the lumen. I think that one of the sections that Dr. West showed from the patient with mitral stenosis contained an altered bronchial rather than a pulmonary vessel.

As regards the question of the flow through the bronchial arteries: When a pulmonary artery becomes occluded by ligature or thrombus, there must be a fall in the capillary blood pressure distal to the occluded vessel. This will result in a greater flow through the bronchial arteries to the same capillary bed and, in consequence of mechanisms not entirely clear, also increase in size.

As regards "selective angiography": It is true one must extend the time of the successive films, since there may be a delay in filling pulmonary arteries leading to diseased tissues. Also these patients should be studied from the lateral as well as postero-anterior aspects, for, when the left lung is shrunken, the course of the pulmonary artery is almost directly backwards, and one may not see it in the postero-anterior film.

The old observations on the passage of radio-opaque material to the normal side only have been confirmed, many times, and I think they must be accepted. We must recognize that when these communications exist between pulmonary and bronchial arterial systems, the flow will go as always from points of higher to lower pressure. There may be changes in pressure under certain circumstances with consequent reversal of flow; it is not always in the same direction, particularly in disease.

As regards Lendrum's paper,[5] I think he was not making a final statement but rather was seeking help in interpreting the peculiar spectacle seen radiographically in which the hemosiderin is seen in punctate distribution, within the bronchioles. He did not know exactly where the hemosiderin came from, whether from bronchial arterioles, or bronchial venules or elsewhere. Unfortunately we have not been able to give him this help, but it is now known that blood introduced intratracheally acquires the same focal distribution. In reference to another question of Dr. Cournand, the enlargement of the bronchial veins in mitral stenosis, in spite of the fact that it occurs in this condition as shown by Ferguson, Kobilak and Deitrick,[6] cannot be easily demonstrated with our method. It is clear that the expansion of the bronchopulmonary veins in emphysema is relatively enormous, even in comparison with what happens in the most severe instances of long-standing mitral stenosis. More must actually underlie this expansion of vessels than mere pressure change, but, once the vessels are increased in size, there exists an extra-pulmonary shunt. This must be taken into account as a possible explanation of certain clinical phenomena, such as sudden cyanosis which occurs in some individuals with cor pulmonale upon digitalization.

As regards Von Hayek's statements about the shunts: This appears to be a matter of arm-chair interpretation on his part. He has drawn analogies on purely anatomic grounds from arteriovenous shunts such as exist elsewhere. Von Hayek thinks that certain segments of the pulmonary or bronchial arteries look like normal anastomoses in the skin and therefore he speculates that they have similar functions in the lung.

In regard to the Chairman's invitation to discuss Dr. West's paper, I would like to express appreciation of a very clear discussion of those aspects of the problem not concerned with the collateral circulation, in other words, those aspects which were mentioned as being of enormous importance but outside the theme of my own remarks, the pulmonary arteries and the capillary beds of the lungs.

JOHN R. WEST: I have very little to add on the subject of pulmonary hypertension. Dr. Cournand has discussed in detail the subject of motor activity of pulmonary blood vessels and has mentioned a great amount of experimental work that has been done. It is important to note in this connection also that a considerable species difference has been noted among various experimental animals used in these studies.

I believe that Dr. Liebow's paper has been discussed by Dr. Cournand far more adequately than I can discuss it. I enjoyed it very much, and I only wish we were able to employ a technique such as his in conjunction with the measurements with which we are chiefly concerned, namely those relating to pulmonary ventilation and gas exchange in acute and chronic pulmonary disease.

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The Pathology of Tay-Sachs' Disease

*Abstracts of Papers**

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During the latter part of the past century Sachs isolated a number of cases from the broad category of infantile mental deficiency, designating them as instances of arrested cerebral development. With his further contact with the disease, salient features emerged which furnished greater individuality to this entity. A familial tendency became apparent; the rapidly developing blindness seen in Sachs' first case was a constantly repetitive observation. Sachs incorporated these defining elements and applied the more appropriate term, amaurotic family idiocy, to the disease.

In the years that have followed newer concepts of the disease have evolved. Descriptions of cases in the late infantile, juvenile and even adult period of life have revealed that the disease cannot be consigned to its original narrow age limit. The seven cases embodied in the present report, however, all fall in the infantile category. The presenting symptoms, with some variation, were quite similar. Arrest and regression of development, apathy, weakness and amaurosis were apparent. Hyperacusis was an outstanding feature in the majority of the cases.

At autopsy only a paucity of alterations was grossly apparent, none bearing any distinctive quality. In some instances the pattern of surface fissuration was overly simplified and the sulci unduly broadened. Gross sectioning of the central nervous system rarely brought to light any additional abnormality. In striking contrast to the meager and non-specific results of gross visualization, microscopic examination disclosed cellular alterations of such universal distribution that no slide of the nervous system failed to exhibit the histopathology distinctive of the disease. The primary cellular alterations resided exclusively in the neurons. All other changes in glial and mesodermal elements were considered as responsive to ganglionic degradation. Neuronal involvement was exclusive and ubiquitous; neurons of the entire autonomic system shared equally in the process. The cytologic sine qua non of Tay-Sachs' disease is an enlarged neuron which has lost its angular configuration. The Nissl substance is diminished in amount, the residuum compressed about an eccentric nucleus. The

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